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Case report

Poorly differentiated high-grade urothelial carcinoma presenting as Paget's disease of the vulva with no overt urinary tract neoplasm detected

Radha R. Padhy [a,b,*,1], Niloo Nasseri-Nik [b], Fouad Abbas [a]

[a] MedStar Harbor Hospital, United States
[b] Johns Hopkins Hospital, United States

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ABSTRACT

Objective: There are few reported cases of secondary (non-cutaneous) vulvar Paget's disease related to urothelial carcinoma (UC), with only 7 of them presenting initially with Paget's disease and up to a 13-year lapse from detecting a urinary tract neoplasm after the onset of symptoms. This is a case of Paget's disease of urothelial origin with no urinary tract neoplasm detected on initial presentation.
Methods: This is a 59-year-old African-American female who presented with worsening eczematous lesions for two years. She had no symptoms suggestive of UC. Initial biopsies showed poorly differentiated high-grade UC with pagetoid changes.
Results: Stains showed immunoreactivity for CK7, uroplakin III, p16 and p63 with negative CK20 expression. This staining pattern is characteristic of pagetoid urothelial intraepithelial lesion, now listed as secondary Paget's disease. Biopsies showed GATTA3 positivity suggestive of urothelial origin. Both GCDFP-15 and CEA were negative, which are normally expressed by Paget cells of the primary (cutaneous) type.
A follow-up cystoscopy was unremarkable. The patient underwent a partial radical vulvectomy with bilateral lymphadenectomy for extensive disease. Final pathology confirmed infiltrating high-grade UC with overlying epidermis displaying pagetoid in-situ tumor component.
Conclusion: This is a rare case of secondary Paget's disease of urothelial origin where there was no concurrent UC nor did the patient present with symptoms suggestive of a urinary tract malignancy. In initial presentations of vulvar Paget's disease, it is important to be aware of the secondary classification because it warrants investigation of surrounding structures to rule out underlying malignancies that are or have not yet become clinically apparent.

1. Introduction

Vulvar Paget's disease is a rare disease that has been classified recently as either primary (cutaneous) or secondary (non-cutaneous) types by Wilkinson and Brown based on the origin of cells (Wilkinson and Brown, 2002). While the primary cutaneous-type arises from intraepidermal pluripotent stem cells and is characterized by atypical glandular-type proliferation of "Paget cells" (large nucleated cells with prominent cytoplasm and nucleoli), the secondary non-cutaneous type is usually a manifestation of adjacent ano-rectal, urothelial or other underlying neoplasms (Wilkinson and Brown, 2002; Brown and Wilkinson, 2002; Kurman et al., 2011). Rarely, primary Paget's disease can also arise from dermal apocrine glands and spread into the overlying epidermis (Wilkinson and Brown, 2002). In this paper, we focus on the distinction between primary cutaneous Paget's disease and Paget's disease of urothelial origin, which is the much rarer occurrence among the secondary non-cutaneous types.

Clinically differentiating these two types can be very difficult because both classically present with chronic pruritic and eczematous vulvar lesions. However, some clinically distinguishing features suggesting urothelial origin have been acknowledged. These include primary involvement of the vulvar vestibule and periurethral vestibular mucosa as key features in addition to the classical labial majora lesions found in primary cutaneous type (Wilkinson and Brown, 2002; Brown and Wilkinson, 2002). Hematoxylin and eosin stains are also non-specific because cellular features in both primary and secondary Paget's disease have very similar morphologies. The similar morphologies necessitate immunohistochemical studies to distinguish between the two (Brown and Wilkinson, 2002; Reyes et al., 2012). However, it has been noted

* Corresponding author at: MedStar Harbor Hospital, 3001 S. Hanover Street, Baltimore, MD 21225, United States.
E-mail address: Rpadhy@northwell.edu (R.R. Padhy).
[1] Present address: Staten Island University Hospital, 475 Seaview Avenue, Staten Island, NY 10305, United States.

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that Paget's disease of urothelial origin has cellular features that resemble high grade urothelial cells with hyperchromatic nuclei, increased mitotic figures and a higher degree of anaplastic characteristics (Wilkinson and Brown, 2002; Reyes et al., 2012).

Very few cases of secondary vulvar Paget's disease related to urothelial carcinoma have been reported, with only 7 of them presenting initially with clinical Paget's disease (Wilkinson and Brown, 2002; Brown and Wilkinson, 2002; Reyes et al., 2012; Degefu et al., 1986). The average time to discovery of a urinary tract neoplasm following the onset of symptoms has ranged anywhere from 1 to 13 years (Kurman et al., 2011; Reyes et al., 2012; Boardman et al., 2001; Powell et al., 1985). The rest of the reported cases have had some form of previously diagnosed urothelial carcinoma, either arising from the bladder, the ureters or urethra.

2. Case presentation

This is a case of a 59-year-old obese African American female who presented with chronic pruritis and progressively worsening eczematous lesions lasting for more than two years. No complaints of dysuria, hematuria, hesitancy, frequency or any other symptoms suggestive of urinary tract malignancy were noted at that time. Family history and past medical history were insignificant for cancer or other comorbid conditions. Initial biopsies performed at an outside institution two years prior were read as pemphigus vulgaris. Patient was treated accordingly with topical steroids and immunosuppressants with no resolution of symptoms. She presented to us two years later with worsening eczematous lesions bilaterally on her vulva for which she underwent a partial radical vulvectomy. Tissue samples showed morphological features suggestive of a poorly differentiated high-grade urothelial carcinoma with pagetoid changes in the underlying mucosa, as shown in Fig. 1.

Stains performed by an outside institution showed immunoreactivity for CK7 and uroplakin III with negative CK20 expression. P16 and p63 were also found to be positive as shown in Fig. 2. This staining pattern has been well described for secondary Paget's disease of urothelial origin (Wilkinson and Brown, 2002; Brown and Wilkinson, 2002; Kurman et al., 2011; Ohnishi and Watanabe, 2000). Furthermore, biopsies showed GATTA3 positivity, which is highly suggestive of a urothelial origin. Both gross cystic disease fluid protein-15 (GCDFP-15) and CEA in this case were negative, which are normally expressed by Paget cells of the primary (cutaneous) type (Reyes et al., 2012). In-situ hybridization for high risk HPV did not detect a signal either.

A follow-up cystoscopy was done to find the source of the neoplastic spread, which was found to be unremarkable for any large infiltrating masses or grossly erythematous lesions. A CT scan also showed normal urinary bladder and kidneys in addition to extensive pelvic and inguinal adenopathy. At that point, the patient's disease was too extensive with full-thickness infiltration of the tumor and positive margins. Therefore, a partial radical vulvectomy with bilateral pelvic lymphadenectomy was performed. Final pathology was unchanged from the initial diagnosis of infiltrating high-grade urothelial carcinoma. There was extensive lymph-vascular invasion in both the dermal and subcutaneous tissues with extension into the margins. The overlying epidermis also displayed ulceration and a pagetoid in-situ tumor component.

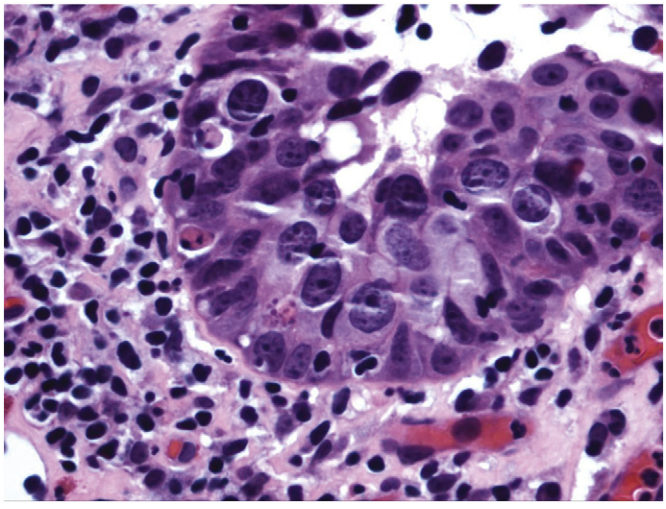

Fig. 1. Vulvar biopsy: A foci of pagetoid cells with abundant cytoplasm and prominent nuclei observed in the background of inflammatory cells within the epidermal layer.

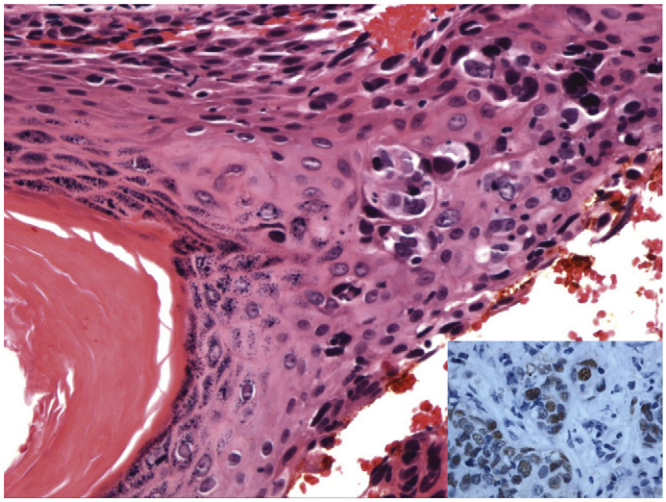

Fig. 2. Vulvar specimen: Pagetoid cells within dermal layer. Inset: Uroplakin III +.

Patient's post-operative course was immediately complicated with acute renal failure requiring nephrostomy tube placement. Renal ultrasound at that time showed bilateral hydronephrosis. Repeat CT imaging showed unchanged pelvic and inguinal adenopathy with no identifiable obstructing mass. The patient's acute kidney failure was attributed to underlying acute tubular necrosis due to labile blood pressures observed immediately after the procedure. She then subsequently presented with bladder atony further requiring bilateral stent placement. Her progressively declining renal function was attributed to the malignant nature of her cancer, and thereafter was put on a conservative chemo-radiation regiment. Three months post-operatively, CT scan showed evidence of liver metastasis, for which she was enrolled in palliative care.

3. Discussion

Secondary (non-cutaneous) Paget's disease is a manifestation of an underlying neoplasm, with urothelial metastatic spread to the vulva being much rarer than the more common renal adenocarcinomas. Majority of the cases follow the sequence of the diagnosis of a primary urinary neoplasm with an occurrence of vulvar Paget's disease sometime later in the future. However, to our knowledge, there have been 7 cases documented so far where Paget's vulvar disease has preceded the discovery of a urothelial neoplasm anywhere from 1 to 14 years (Wilkinson and Brown, 2002; Brown and Wilkinson, 2002; Reyes et al., 2012; Degefu et al., 1986).

In one of the earliest studies done by Powell et al. describing patients with both genital Paget's disease and urinary tract malignancy, 3 out of 8 cases initially presented with clinical Paget's disease which were then followed by the discovery of transitional cell carcinoma (TCC) of the bladder at 3, 8 and 13 years (Powell et al., 1985). Three other cases had already had previously diagnosed TCC of the bladder with subsequent development of vulvar Paget's disease attributed to the pagetoid epidermal spread from the primary urothelial neoplasm (Powell et al., 1985). Only an association was described between the two different

Table 1
Reported cases of Paget's disease as initial presentation followed by detection of urothelial malignancy.

Study	Total patients studied	Patient	Initial presentation/Diagnosis	Treatment	Urothelial malignancy detected	Time between initial detection of vulvar Paget's disease and subsequent detection of urothelial malignancy
Boardman et al. (2001)	2	1	Vulvar Paget disease	Wide local excision	Urothelial CIS	14 y
Degefu et al. (1986)	1	2	Vulvar Paget disease	Simple vulvectomy	Papillary TCC of kidney and ureter	1 y
Kurman et al. (2011)	3	3	Vulvar Paget's disease	Partial vulvectomy	Poorly differentiated carcinoma of bladder and urethra	4 y
Powell et al. (1985)	8	4	Vulvar Paget's disease	Not specified	TCC of bladder	8 y
		5	Vulvar Paget's disease	Not specified	TCC of bladder, ureter, urethra	3 y
		6	Vulvar Paget's disease	Not specified	Papillary TCC of bladder	13 y
Arnould et al. (1998)	6	7	Vulvar Paget's disease	Radical vulvectomy	Bladder CIS	1 y
Padhy et al.	1	1	Vulvar Paget's disease	Wide local excision	Urothelial carcinoma	2 y

disease entities at that time with no causal relationship established. Four other cases have been reported in future studies and are listed in Table 1.

Histopathologically, the association between urothelial carcinoma and Paget's disease has been documented as either separate occurrences that are histologically distinct, or as pagetoid extensions into the vulva from a primary urothelial carcinoma (Arnould et al., 1998).

In the cases with underlying bladder neoplasms and later occurrences of vulvar Paget's disease, there have been either cystoscopic or CT evidence of a genitourinary lesion or mass documented (Wilkinson and Brown, 2002; Reyes et al., 2012). The vulvar involvement in these cases have shown Paget cell features with pagetoid growth along the basal layers in the background of neoplastic cells (Wilkinson and Brown, 2002; Reyes et al., 2012) This case is unique in that there were no overt lesions noted on cystoscopy nor did the patient present with any signs of hematuria, hesitancy or frequency suggestive of a urinary tract neoplasm.

Even in the first ever reported case of vulvar Paget's disease associated with primary urothelial malignancy by Degefu et al. the patient had presented with hematuria prior to her clinical Paget's disease for which a full diagnostic work-up revealed no urothelial malignancy (Degefu et al., 1986).

Certain immunohistochemical stains have recently been shown to be more specific in identifying the urothelial origin of cells in secondary Paget's disease, namely uroplakin III and p63. Brown and Wilkinson reported the efficiency of uroplakin III (UIII) in differentiating primary from secondary Paget's disease being that it is a highly specific stain for primary and metastatic urothelial carcinomas (Brown and Wilkinson, 2002). In their study of 17 patients, all cases of secondary Paget's disease of urothelial origin showed strong UIII cytoplasmic staining whereas none of the cases of primary Paget's disease showed UIII immunoreactivity (Brown and Wilkinson, 2002). Yanai et al. further documented the use of p63 in distinguishing primary from secondary Paget's disease in the setting of negative uroplakin III immunoreactivity, with strong positivity noted in secondary Paget's disease of urothelial origin (Yanai et al., 2008). In our case, both p63 and uroplakin III were positive.

4. Conclusion

This is the first case report of secondary Paget's disease of urothelial origin where there has been no overt urinary tract malignancies noted on cystoscopy nor did the patient present with symptoms suggestive of a urinary tract malignancy.

In initial presentations of vulvar Paget's disease, it is important to be aware of the secondary (non-cutaneous) classification because it warrants investigation of surrounding structures to rule out underlying malignancies that are or have not yet become clinically apparent. Secondary (non-cutaneous) vulvar Paget's disease of urothelial origin is described as a manifestation of urothelial neoplasia, but up to 7 cases have been reported with Paget's disease being the initial presentation and preceding detection of a urinary tract neoplasm by almost 14 years (Powell et al., 1985). This prolonged detection period warrants close follow-up of such patients with cystoscopies more routinely incorporated into their follow-up courses similar to surveillance recommendations for urothelial carcinoma (National Comprehensive Cancer Network). Furthermore, accurate diagnosis of secondary (non-cutaneous) Paget's disease is important because current literature recommends that pagetoid lesions of urothelial origin should be recognized as intraepithelial non-invasive lesions, and therefore treatment should be aimed at the primary site neoplasm (Wilkinson and Brown, 2002; Brown and Wilkinson, 2005).

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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